# General

## Guideline Title

(1) The treatment of central sleep apnea syndromes in adults: practice parameters with an evidence-based literature review and meta-analyses. (2) Updated adaptive servo-ventilation recommendations for the 2012 AASM guideline: "The treatment of central sleep apnea syndromes in adults: practice parameters with an evidence-based literature review and meta-analyses."

## Bibliographic Source(s)


Aurora RN, Bista SR, Casey KR, Chowdhuri S, Kristo DA, Mallea JM, Ramar K, Rowley JA, Zak RS, Heald JL. Updated adaptive servo-ventilation recommendations for the 2012 AASM Guideline: "The treatment of central sleep apnea syndromes in adults: practice parameters with an evidence-based literature review and meta-analyses". J Clin Sleep Med. 2016 May 15;12(5):757-61. [33 references] PubMed

Aurora RN, Chowdhuri S, Ramar K, Bista SR, Casey KR, Lamm CI, Kristo DA, Mallea JM, Rowley JA, Zak RS, Tracy SL. The treatment of central sleep apnea syndromes in adults: practice parameters with an evidence-based literature review and meta-analyses. Sleep. 2012 Jan 1;35(1):17-40. [112 references] PubMed


## Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

# Recommendations

## Major Recommendations

Note from the National Guideline Clearinghouse (NGC) and the American Academy of Sleep Medicine (AASM): In 2016, AASM performed a focused update of the 2012 systematic review and meta-analyses to update the recommendation for the use of adaptive servo-ventilation (ASV) for the treatment of central sleep apnea syndrome (CSAS) related to congestive heart failure (CHF). The updated recommendations are labeled "2016 Focused Update."

The levels of evidence (high, moderate, low, very low) and levels of recommendation (standard, guideline, option) are defined at the end of the "Major Recommendations" field.

2012 Guideline

Treatment of CSAS

*Primary CSAS*

Positive airway pressure therapy may be considered for the treatment of primary CSAS. (OPTION)

*Values and Trade-offs: The literature on the use of positive airway pressure (PAP) therapy (continuous positive airway pressure [CPAP], bilevel positive airway pressure in a spontaneous-timed mode [BPAP-ST], ASV) for the treatment of primary CSAS is very limited. However, PAP therapy offers the following benefits: (1) it has the potential to ameliorate central respiratory events; (2) it typically does not confer significant risks; and (3) it is readily available in most centers. Therefore, PAP therapy can be considered for the treatment of primary CSAS. The overall very low level of quality of evidence rendered an OPTION level recommendation.*

Acetazolamide has limited supporting evidence but may be considered for the treatment of primary CSAS. (OPTION)

*Values and Trade-offs: Given the low overall quality of evidence and the potential for side effects including paresthesias, tinnitus, gastrointestinal symptoms, metabolic acidosis, electrolyte imbalance, and drowsiness, the use of acetazolamide for the treatment of primary CSAS received an OPTION level recommendation.*

The use of zolpidem and triazolam may be considered for the treatment of primary CSAS only if the patient does not have underlying risk factors for respiratory depression. (OPTION)

*Values and Trade-offs: Due to the limited available evidence and the significant potential for adverse side effects especially respiratory depression, the use of zolpidem and triazolam in the setting of primary CSAS is not a preferable option and remains the last therapeutic option, to be considered only if the other therapeutic options listed above fail. Very close clinical follow-up must be provided to consider the use of these hypnotic agents.*

*CSAS Due to CHF Including Cheyne Stokes Breathing Pattern (CSBP) and Not Cheyne Stokes Breathing*

CPAP therapy targeted to normalize the apnea-hypopnea index (AHI) is indicated for the initial treatment of CSAS related to CHF. (STANDARD)

*Values and Trade-offs: The overall quality of evidence for the use of CPAP in the setting of CSAS related to CHF is moderate, but with a large effect size and consistent findings for reduction of AHI and improvement in left ventricular ejection fraction (LVEF). Post hoc analysis of the Canadian continuous positive airway pressure (CANPAP) data indicates that CPAP treatment targeted to an AHI <15 has a positive effect on transplant-free survival in patients with CSAS and CHF. Given the relative ease of availability of this therapeutic intervention and overall familiarity with its use, a STANDARD level of recommendation was given. An alternate treatment option should be considered in the absence of adequate control of CSAS related to CHF with CPAP.*

BPAP therapy *in a spontaneous timed (ST)* mode targeted to normalize the AHI may be considered for the treatment of CSAS related to CHF only if there is no response to adequate trials of CPAP, ASV, and oxygen therapies. (OPTION)

*Values and Trade-offs: There were a limited number of studies that examined the effectiveness of BPAP in the treatment of CSAS/CSR. ST mode was used more frequently compared with spontaneous mode in the available studies. The level of evidence for BPAP with spontaneous mode is comprised only of 1 trial that met inclusion criteria. Therefore, no recommendation can be made for this mode of BPAP until further evidence is available. BPAP-ST therapy offers many of the same advantages as CPAP therapy, such as low risk and easy availability. BPAP-ST may be considered only in those who fail CPAP, ASV, and oxygen therapy, as these latter options have substantially more evidence supporting their use. BPAP-ST is a form of noninvasive ventilation that requires specialized expertise. The cost is approximately $1900 compared with $400-$1000 for CPAP. The paucity of data allows only an OPTION level of recommendation at this time.*

Nocturnal oxygen therapy is indicated for the treatment of CSAS related to CHF. (STANDARD)

*Values and Trade-offs: Based on data presented in the original guideline document, the benefits of oxygen supplementation for the treatment of CSAS are abundant and outweigh any potential disadvantages. While the variable duration of treatment in each study limits recommendations in regard to duration of oxygen therapy, the overall positive direction of results with respect to reducing AHI and improving LVEF confirms the recommendation. Although 1 paper reported that the cumulative incidence rate of cardiac events was no different between oxygen therapy and control groups, its effect on transplant free survival has not been assessed. The universal availability of oxygen therapy coupled with the overall quality of evidence discussed above influenced the level of recommendation. It should be noted that while oxygen therapy does not confer outcome advantages over CPAP therapy in the available evidence, supplemental oxygen can be easily administered and can be given for those individuals with CSAS related to CHF who are unable to comply with CPAP therapy. Consideration should be given to a repeat sleep study with oxygen to ensure adequate resolution of central sleep apnea events. In the US, the current cost of supplemental oxygen therapy is approximately $200 per month.*

The following therapies have limited supporting evidence but may be considered for the treatment of CSAS related to CHF, after optimization of standard medical therapy, if PAP therapy is not tolerated, and if accompanied by close clinical follow-up: acetazolamide and theophylline. (OPTION)

*Values and Trade-offs: There is only 1 study for acetazolamide and 2 studies for theophylline. Therefore the data for each agent are very low. Furthermore, the benefits vs. harms are unclear. Side effects of acetazolamide have been previously outlined. Theophylline is also associated with a number of potential adverse effects such as cardiac arrhythmias, central nervous system (CNS) excitability, and gastrointestinal symptoms. Additionally, it has a narrow therapeutic index, and therefore close monitoring of levels is important. These pharmacological therapies require further research to generate more confidence in their effectiveness and to justify more than an OPTION level of recommendation.*

*CSAS Due to Medical Condition Not Cheyne Stokes: End-Stage Renal Disease (ESRD)*

The following possible treatment options for CSAS related to end stage renal disease may be considered: CPAP, supplemental oxygen, bicarbonate buffer use during dialysis, and nocturnal dialysis. (OPTION)

*Values and Trade-offs: At this time, the level of evidence is very low and the estimate of benefits vs. harms is unclear regarding any specific mode of therapy in ESRD patients with CSAS; therefore, an OPTION level of recommendation has been accorded. However, despite the very low level of evidence, it is clear that bicarbonate buffer is preferable during hemodialysis in these patients. Further studies are needed to elucidate the role of oxygen, CPAP, bicarbonate buffer use during dialysis, and nocturnal hemodialysis in patients with ESRD.*

2016 Focused Update

ASV for the Treatment of CSAS Related to CHF

ASV targeted to normalize the AHI should not be used for the treatment of CSAS related to CHF in adults with an ejection fraction ≤45% and moderate or severe CSA predominant, sleep-disordered breathing. (STANDARD AGAINST)

ASV targeted to normalize the AHI can be used for the treatment of CSAS related to CHF in adults with an ejection fraction >45% or mild CHF-related CSAS. (OPTION)

*Values and Tradeoffs: Although there is only one study demonstrating a small but statistically significant increase in mortality with ASV use in CHF patients with an EF ≤45% and moderate or severe CSA, the strength of the evidence is high given the study design, duration of follow-up, and sample size. Thus, at this time, ASV therapy should not be prescribed to heart failure patients with moderate or severe CSA predominant, sleep-disordered breathing (SDB), and an ejection fraction ≤45%. However, the results from this singular study cannot be generalized to other types of heart failure, i.e., those with preserved ejection fraction (EF >45%), mild sleep-disordered breathing, or those with obstructive sleep apnea (OSA)-predominant SDB. It is also recommended that until further data are available, other ASV devices not be prescribed for the subgroup of heart failure patients with an ejection fraction ≤45% and moderate or severe central sleep apnea.*

Definitions

2012 Guideline

*Summary of Grading of Recommendations Assessment, Development and Evaluation (GRADE) Approach to Rating Quality of Evidence**

| Study Design | Initial Quality of a Body of Evidence | Lower if | Higher if | Quality of a Body of Evidence |
|---|---|---|---|---|
| Randomized trials | High → | Risk of bias<br>−1 Serious<br>−2 Very serious | Large effect<br>+1 Large<br>+2 Very large | High (four plus: ++++) |
| | | Inconsistency<br>−1 Serious<br>−2 Very serious | Dose response<br>+1 Evidence of a gradient | Moderate (three plus: +++O) |
| Observational | Low → | Indirectness | All plausible residual confounding | Low (two plus: ++OO) |

| Study Design | Initial Quality of a Body of Evidence | Lower if | Higher if | Quality of a Body of Evidence |
|---|---|---|---|---|
| studies | | −2 Very serious | +1 Would reduce a demonstrated effect | |
| | | Imprecision −1 Serious −2 Very serious Publication bias −1 Likely −2 Very likely | +1 Would suggest a spurious effect if no effect was observed | Very Low (one plus: +OOO) |

*Final Assessments of Level of Bodies of Evidence**

High: The guideline developers are very confident that the true effect lies close to that of the estimate of the effect.

Moderate: The guideline developers are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low: The confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low: The guideline developers have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

*From Balshem H, Helfand M, Schunemann H, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011;64:401-6.

2016 Focused Update

The assessment of evidence quality was performed by American Academy of Sleep Medicine (AASM) staff and the task force. The task force followed the GRADE process that was used in the 2012 Practice Parameters, with slight modifications to the initial quality rating based on recent publications from the GRADE working group. The results are reported in Table S1 in the supplemental material (see the "Availability of Companion Documents" field).

*American Academy of Sleep Medicine (AASM) Strengths of Recommendations*

| Assessment of Benefits vs. Harms/Burdens | Overall Quality of Evidence | | | |
|---|---|---|---|---|
| | High | Moderate | Low | Very Low |
| Benefits clearly outweigh harms/burdens | Standard | Standard | Guideline | Option |
| Benefits closely balanced with harms/burdens OR Uncertainty in the estimates of benefits vs harms/burdens | Guideline | Guideline | Option | Option |
| Harms/burdens clearly outweighs benefits | Standard | Standard | Standard | Standard |

## Clinical Algorithm(s)

None provided

# Scope

## Disease/Condition(s)

Central sleep apnea syndrome (CSAS)

- Primary central sleep apnea
- Central sleep apnea due to Cheyne Stokes breathing pattern

- Central sleep apnea due to medical condition not Cheyne Stokes
- Central sleep apnea due to high-altitude periodic breathing
- Central sleep apnea due to drug or substance

Note: Primary sleep apnea of infancy is not considered in this guideline.

## Guideline Category

Assessment of Therapeutic Effectiveness

Evaluation

Management

Treatment

## Clinical Specialty

Cardiology

Family Practice

Internal Medicine

Pulmonary Medicine

Sleep Medicine

## Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Respiratory Care Practitioners

## Guideline Objective(s)

2012 Guideline

To review the available data for the treatment and management of central sleep apnea syndromes (CSAS) in adults

2016 Focused Update

To update the specific recommendations from the 2012 practice parameter paper pertaining to the use of adaptive servo-ventilation (ASV) to treat CSAS associated with congestive heart failure

## Target Population

2012 Guideline

Adults with central sleep apnea syndromes (CSAS)

2016 Focused Update

Adults with CSAS and congestive heart failure using adaptive servo-ventilation

## Interventions and Practices Considered

1. Continuous positive airway pressure (CPAP)
2. Bilevel positive airway pressure (BPAP)
3. Adaptive servo-ventilation (ASV)
4. Oxygen therapy
5. Acetazolamide
6. Theophylline
7. Zolpidem
8. Triazolam
9. Bicarbonate buffer use during dialysis and nocturnal dialysis for central sleep apnea syndromes related to end-stage renal disease

Note: The following interventions were considered but no recommendation for use was made: carvedilol, captopril, erythropoietin, intravenous iron, carbon dioxide, cardiac interventions: cardiac resynchronization therapy (CRT), atrial overdrive pacing (AOP).

## Major Outcomes Considered

2012 Guideline

- Morbidity and mortality
- Chance of congestive heart failure (CHF)
- Left ventricular ejection fraction (LVEF)
- Transplant-free survival in patients with CHF
- Apnea-hypopnea index (AHI)
- Severity of disease

2016 Focused Update

- Mortality (cardiac death)
- LVEF
- AHI
- Absolute effects of treatments

# Methodology

## Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

## Description of Methods Used to Collect/Select the Evidence

2012 Guideline

Literature Search

A search for articles on the medical treatment of central sleep apnea syndromes (CSAS) was conducted using the PubMed database from 1966 through June 2010. The key words for searches were: (central sleep apnea treatment), (Cheyne-Stokes treatment), [(central sleep apnea) and (heart failure) and treatment], [(sleep apnea) and narcotics and treatment], and [(sleep-related breathing disorders) and narcotics and treatment]. The limits on these searches were humans, English, adults (+19 years), clinical trials, meta-analyses, and randomized controlled trials. A second set of more specific searches was done with the limits of humans, English, and adults (+19 years) with (central sleep apnea) and the following terms: 1) high altitude, 2) opioid, 3) traumatic brain injury, 4) [(end stage renal disease) or (renal disease) or ESRD], and pharmacotherapy. The search was

updated in June 2010 to include the latest research publications. Abstracts from these articles were reviewed to determine if they met inclusion criteria, which were a minimum of 5 patients plus clinical outcomes measures of mortality/transplant-free survival, left ventricular ejection fraction (LVEF), or apnea-hypopnea index (AHI). Complex sleep apnea was not included, as it is not currently listed as a disorder in the International Classification of Sleep Disorders, Second Edition (ICSD-2). Additionally, sleep disordered breathing had to be clearly differentiated between CSAS and obstructive sleep apnea (OSA). CSAS was defined as greater than 50% central events including periodic breathing if subjects presented with both CSAS and OSA. Additional articles were identified by pearling (i.e., checking the reference sections of search results for articles otherwise missed).

2016 Focused Update

Literature Searches

A literature search was performed on November 15, 2015 by the American Academy of Sleep Medicine (AASM) research staff using the PubMed database (see Figure 1 in the original guideline document), using the following criteria:

- Adaptive servo-ventilation (ASV) AND
- Sleep apnea syndromes AND
- Articles published from June 2010–present AND
- Limits of adults 19+, English, and humans

This resulted in 51 publications. Full keywords and MeSH terms for the literature search can be found in the appendix (see supplemental material, "Literature Search String") (see the "Availability of Companion Documents" field). Abstracts from all retrieved articles, including "pearled" publications, were individually assessed by two task force (TF) members to determine whether the publication should be included for further consideration in the project. Inclusion criteria were:

- A minimum of 5 patients plus clinical outcomes measures of mortality/transplant-free survival, LVEF, or AHI AND
- Sleep-disordered breathing is clearly differentiated between CSA and OSA AND
- The central sleep apnea index is greater than the obstructive sleep apnea index OR the percentage of central events is greater than 50% of respiratory events

## Number of Source Documents

2012 Guideline

A total of 252 articles were identified, but only 77 articles met the specific inclusion criteria for this guideline and were reviewed, graded, and extracted.

2016 Focused Update

Twenty new studies were approved for inclusion. Of the studies used for the 2012 practice parameters, 9 were included, for a total of 29 studies included in the new evidence base. Twenty-seven were used for the meta-analysis.

## Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

## Rating Scheme for the Strength of the Evidence

2012 Guideline

Summary of Grading of Recommendations Assessment, Development and Evaluation (GRADE) Approach to Rating Quality of Evidence*

| Study Design | Initial Quality of a Body of Evidence | Lower if | Higher if | Quality of a Body of Evidence |
|---|---|---|---|---|
| Randomized trials | High → | Risk of bias<br>−1 Serious | Large effect<br>+1 Large | High (four plus: ++++) |

| Study Design | Initial Quality of a Body of Evidence | Lower if | Higher if | Quality of a Body of Evidence |
|---|---|---|---|---|
| | | −2 Very serious | +2 Very large | |
| | | Inconsistency<br>−1 Serious<br>−2 Very serious | Dose response<br>+1 Evidence of a gradient | Moderate (three plus: +++O) |
| Observational studies | Low → | Indirectness<br>−1 Serious<br>−2 Very serious | All plausible residual confounding<br>+1 Would reduce a demonstrated effect | Low (two plus: ++OO) |
| | | Imprecision<br>−1 Serious<br>−2 Very serious<br>Publication bias<br>−1 Likely<br>−2 Very likely | +1 Would suggest a spurious effect if no effect was observed | Very Low (one plus: +OOO) |

Final Assessments of Level of Bodies of Evidence*

High: The guideline developers are very confident that the true effect lies close to that of the estimate of the effect.

Moderate: The guideline developers are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low: The confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low: The guideline developers have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

*From Balshem H, Helfand M, Schunemann H, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol.* 2011;64:401-6.

2016 Focused Update

The assessment of evidence quality was performed by American Academy of Sleep Medicine (AASM) staff and the task force. The task force followed the GRADE process that was used in the 2012 Practice Parameters, with slight modifications to the initial quality rating based on recent publications from the GRADE working group.

## Methods Used to Analyze the Evidence

Meta-Analysis

Systematic Review with Evidence Tables

## Description of the Methods Used to Analyze the Evidence

2012 Guideline

Quality of Evidence

The assessment of evidence quality was performed according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process. The GRADE system differs from other grading systems as each study is not only evaluated for study design and risk of bias, but, additionally, an estimate of effect (see footnote A in the original guideline document) is generated for each outcome. Multiple aspects of quality are assessed including study limitations, imprecision, inconsistency of results, indirectness of evidence, and likeliness of publication bias. The quality of effects from observational studies can be adjusted by the presence of large magnitudes of effect, evidence of dose-response associations, and the presence of confounders. Quality refers to the confidence that the estimates of the effects are correct, and the quality rating is applied to a body

of evidence and not to individual studies.

Briefly, risk of bias includes aspects of study design (randomized control trials [RCTs] versus non-randomized controlled trials or before-after trials) and conduct such as blinding, allocation concealment, large loss to follow up, or selective outcome reporting. Imprecision refers to wide confidence intervals around the estimate of effect when there are relatively few patients and few events. Indirectness occurs when the question being addressed is different than the available evidence regarding population, intervention, comparator, or outcome. There is inconsistency when there is unexplained heterogeneity of the results. Reporting bias can occur if there is selective reporting of studies or outcomes, which may occur if the published evidence is limited to a small number of trials funded by a for-profit organization.

As a first step, all individual studies were assessed by 2 task force members for study design and limitations to validity (bias) for each outcome of interest. RCTs were considered a higher level of evidence than observational, nonrandomized, or before-after interventional studies (see the "Rating Scheme for the Strength of the Evidence" field). Blinding for objective outcomes (mortality, apnea-hypopnea index [AHI], if scoring was blinded) was not considered a threat to internal validity. Subsequently, the body of evidence for each outcome was assessed and graded, taking into account the results of the meta-analysis (if applicable) and other factors as described above. The final assessment, as defined in the "Rating Scheme for the Strength of the Evidence" field, was determined for each treatment and outcome measure.

The results are reported in summary tables in each section of the original guideline document that include the number of studies, study design, limitations, inconsistency, indirectness, imprecision, and other considerations that went into the quality of evidence for each outcome of interest. Also reported are the number of patients that were studied, the overall effect that was calculated in the meta-analysis (reported as the mean difference [MD]), and a qualitative assessment of the relative importance of the outcome.

Meta-Analysis

All meta-analyses were performed using MIX software. The analyses were performed on the AHI and the left ventricular ejection fraction (LVEF) when available. All analyses are presented using the random effects model.

The result of each meta-analysis is shown in a figure with several components in the original guideline document. Each study of the meta-analysis is identified along the left-hand column, and adjacent to it is the year of the study, treatment (exposed, "e") results, and control ("c") results. The results are expressed as "n/M/SD" corresponding to "number/mean/standard deviation." A graphical representation of the data is shown in the center of the figure. The vertical red line indicates the average response of all studies. The zero line represents no effect. The width of the red diamond at the bottom of the plot represents the standard deviation of the meta-analysis. If the red diamond does not touch the zero line, the meta-analysis results indicate that the treatment is different from zero (i.e., it has an effect). The magnitude of the effect across all studies is given by the value of the association measure along with the 95% confidence intervals.

Tables of the data used in the meta-analyses are presented at the end of the manuscript in the appendix in the original guideline document.

2016 Focused Update

Full texts of accepted articles were inspected closely; data pertaining to the outcomes of interest were extracted into spreadsheets by AASM staff. If outcome data were not presented in the format necessary for statistical analysis (i.e., mean, standard deviation, and sample size), the paper was discussed but not used in the meta-analyses.

Statistical and Meta-Analysis

For the outcomes of interest, data from baseline and last treatment time points were used for all statistical and meta-analyses. For adverse events, all data presented in the included papers were used for statistical and meta-analysis. All calculations and meta-analyses were performed using Review Manager 5.3 software. Whenever possible, meta-analyses were performed by pooling data across studies for each outcome and adverse event. The evidence was grouped for analysis based on the clinical outcome of interest and LVEF inclusion criteria (≤45% and >45%).

Meta-analyses for continuous outcomes were performed as pre-post analyses using the random effects model, while relative risk was used for dichotomous outcomes. For most interventions, absolute effects of treatments are represented by the MD ± standard deviation (SD) of posttreatment vs post-placebo. The result of each meta-analysis is displayed as a forest plot. Pooled results for continuous outcomes are expressed as the total number of patients, MD and 95% confidence interval (CI) between the experimental treatment and placebo. Relative risk is presented as baseline risk of the control group (events per thousand) and comparative risk of the intervention (events per thousand).

Strength of Recommendations

The assessment of evidence quality was performed by American Academy of Sleep Medicine (AASM) staff and the task force. The task force followed the GRADE process that was used in the 2012 Practice Parameters, with slight modifications to the initial quality rating based on recent

publications from the GRADE working group. The results are reported in Table S1 in the supplemental material (see the "Availability of Companion Documents" field).

Briefly, risk of bias includes aspects of study design (RCTs versus non-randomized controlled trials or before-after trials) and conduct such as blinding, allocation concealment, large loss to follow up, or selective outcome reporting. Imprecision refers to wide confidence intervals around the estimate of effect when there are relatively few patients and few events. Indirectness occurs when the question being addressed is different than the available evidence regarding population, intervention, comparator, or outcome. There is inconsistency when there is unexplained heterogeneity of the results. Reporting bias can occur if there is selective reporting of studies or outcomes, which may occur if the published evidence is limited to a small number of trials funded by a for-profit organization.

To determine the strength of the recommendation, the task force assessed the quality of evidence and the balance of beneficial and harmful effects.

## Methods Used to Formulate the Recommendations

Expert Consensus

## Description of Methods Used to Formulate the Recommendations

2012 Guideline

The assessment of evidence quality was performed according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) process. All individual studies were evaluated for study design, risk of bias, and an estimate of effect for each outcome measure. Multiple aspects of quality are assessed for bodies of evidence, including study limitations, imprecision, inconsistency of results, indirectness of evidence, and likeliness of publication bias. Bodies of evidence were assessed to be high, moderate, low, or very low (see Box 2 in the original guideline document).

Definitions of levels of recommendations used by the American Academy of Sleep Medicine (AASM) appear in the table in the "Rating Scheme for the Strength of the Recommendations" field. Particularly noteworthy on this table is that when harm/burden clearly outweighs benefit, a STANDARD level of recommendation against the proposed therapy is given regardless of the overall quality of evidence. Sections titled "Values and Trade-offs" appear under each individual practice parameter. The Values and Trade-offs discussion elucidates the rationale leading to each recommendation. These sections are an integral part of the GRADE system and offer transparency to the process.

2016 Focused Update

Expert Task Force

In order to develop this recommendation update, the AASM re-commissioned the authors of the 2012 Practice Parameters paper and the AASM Science and Research Department staff members.

## Rating Scheme for the Strength of the Recommendations

American Academy of Sleep Medicine (AASM) Strengths of Recommendations

| **Assessment of Benefits vs. Harms/Burdens** | **Overall Quality of Evidence** | | | |
|---|---|---|---|---|
| | **High** | **Moderate** | **Low** | **Very Low** |
| Benefits clearly outweigh harms/burdens | Standard | Standard | Guideline | Option |
| Benefits closely balanced with harms/burdens OR<br>Uncertainty in the estimates of benefits vs harms/burdens | Guideline | Guideline | Option | Option |
| Harms/burdens clearly outweighs benefits | Standard | Standard | Standard | Standard |

## Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

## Method of Guideline Validation

External Peer Review

Internal Peer Review

## Description of Method of Guideline Validation

2012 Guideline

The Standards of Practice Committee (SPC) of the American Academy of Sleep Medicine (AASM) developed and the Board of Directors of the AASM approved these practice parameters. The recommendations were also critically reviewed by 2 outside experts, and the concerns that were raised were addressed by the SPC prior to approval by the Board.

2016 Focused Update

Approval and Interpretation of Recommendations

The final guideline was submitted to the AASM Board of Directors who approved these recommendations.

# Evidence Supporting the Recommendations

## Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

# Benefits/Harms of Implementing the Guideline Recommendations

## Potential Benefits

2012 Guideline

- Positive airway pressure (PAP) therapy offers the following benefits: (1) it has the potential to ameliorate central respiratory events; (2) it typically does not confer significant risks; (3) it is readily available in most centers; (4) it reduces apnea-hypopnea index (AHI) and improves left ventricular ejection fraction (LVEF) in the setting of central sleep apnea syndromes (CSAS) related to congestive heart failure (CHF); and (5) it has a positive effect on transplant-free survival in patients with CSAS and CHF.
- Adaptive servo-ventilation (ASV) consistently showed improvement in both the AHI and LVEF when treating CSAS related to CHF. There is also overall better compliance with ASV than continuous positive airway pressure (CPAP).
- The benefits of oxygen supplementation for the treatment of CSAS are abundant and outweigh any potential disadvantages. While the variable duration of treatment in each study limits recommendations in regard to duration of oxygen therapy, the overall positive direction of results with respect to reducing AHI and improving LVEF confirms the developers' recommendation.

Refer to the "Values and Trade-offs" sections under each parameter in the "Major Recommendations" section for specific information on potential benefits of individual treatments.

2016 Focused Update

ASV consistently showed improvement in both the AHI and LVEF when treating CSAS related to CHF.

Refer to the "Values and Trade-offs" section under the parameter in the "Major Recommendations" section for specific information on potential benefits of individual treatments.

## Potential Harms

2012 Guideline

- Acetazolamide has the potential for side effects including paresthesias, tinnitus, gastrointestinal symptoms, metabolic acidosis, electrolyte imbalance, and drowsiness.
- Theophylline is associated with a number of potential adverse effects such as cardiac arrhythmias, central nervous system (CNS) excitability, and gastrointestinal symptoms. Additionally, it has a narrow therapeutic index, and therefore close monitoring of levels is important.
- Due to the limited available evidence and the significant potential for adverse side effects especially respiratory depression, the use of zolpidem and triazolam in the setting of primary central sleep apnea syndromes (CSAS) is not a preferable option and remains the last therapeutic option, to be considered only if the other therapeutic options listed in the guideline fail. Very close clinical follow-up must be provided to consider the use of these hypnotic agents.

2016 Focused Update

In patients with a left ventricular ejection fraction (LVEF) ≤45% and moderate or severe CSA, adaptive servo-ventilation (ASV) has been associated with increased incidence of cardiac death, compared with patients receiving standard care.

# Qualifying Statements

## Qualifying Statements

2012 Guideline

These practice parameters define principles of practice that should meet the needs of most patients in most situations. These guidelines should not, however, be considered inclusive of all proper methods of care or exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding propriety of any specific care must be made by the physician, in light of the individual circumstances presented by the patient, available diagnostic tools, accessible treatment options, and resources.

2016 Focused Update

- The recommendations in this guideline define principles of practice that should complement the 2012 Practice Parameters to meet the needs of most patients in most situations. This guideline should not, however, be considered inclusive of all proper methods of care or exclusive of other methods of care reasonably used to obtain the same results. The ultimate judgment regarding propriety of any specific care must be made by the clinician, in light of the individual circumstances presented by the patient, available diagnostic tools, accessible treatment options, and resources.
- The American Academy of Sleep Medicine (AASM) expects this guideline to have an impact on professional behavior, patient outcomes, and, possibly, health care costs. This clinical practice guideline reflects the state of knowledge at the time of publication and will be reviewed and updated as new information becomes available.

# Implementation of the Guideline

## Description of Implementation Strategy

An implementation strategy was not provided.

## Implementation Tools

Staff Training/Competency Material

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

# Institute of Medicine (IOM) National Healthcare Quality Report

# Categories

## IOM Care Need

Living with Illness

Staying Healthy

## IOM Domain

Effectiveness

Patient-centeredness

# Identifying Information and Availability

## Bibliographic Source(s)

Aurora RN, Bista SR, Casey KR, Chowdhuri S, Kristo DA, Mallea JM, Ramar K, Rowley JA, Zak RS, Heald JL. Updated adaptive servo-ventilation recommendations for the 2012 AASM Guideline: "The treatment of central sleep apnea syndromes in adults: practice parameters with an evidence-based literature review and meta-analyses". J Clin Sleep Med. 2016 May 15;12(5):757-61. [33 references] PubMed

Aurora RN, Chowdhuri S, Ramar K, Bista SR, Casey KR, Lamm CI, Kristo DA, Mallea JM, Rowley JA, Zak RS, Tracy SL. The treatment of central sleep apnea syndromes in adults: practice parameters with an evidence-based literature review and meta-analyses. Sleep. 2012 Jan 1;35(1):17-40. [112 references] PubMed

## Adaptation

Not applicable: The guideline was not adapted from another source.

## Date Released

2012 Jan 1 (addendum released 2016 May 15)

## Guideline Developer(s)

American Academy of Sleep Medicine - Professional Association

## Source(s) of Funding

This is not an industry supported study.

## Guideline Committee

Standards of Practice Committee

## Composition of Group That Authored the Guideline

2012 Guideline

*Committee Members*: R. Nisha Aurora, MD; Susmita Chowdhuri, MD; Kannan Ramar, MD; Sabin R. Bista, MD; Kenneth R. Casey, MD, MPH; Carin I. Lamm, MD; David A. Kristo, MD; Jorge M. Mallea, MD; James A. Rowley, MD; Rochelle S. Zak, MD; Sharon L. Tracy, PhD

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## Financial Disclosures/Conflicts of Interest

2012 Guideline

All members of the American Academy of Sleep Medicine (AASM) Standards of Practice Committee (SPC) and Board of Directors completed detailed conflict-of-interest statements and were found to have no conflicts of interest with regard to this subject.

The authors have indicated no financial conflicts of interest.

2016 Focused Update

Prior to appointment, the authors were required to disclose all potential conflicts of interest (COI) according to the AASM's policy.

This was not an industry supported study. Drs. Kristo and Ramar serve on the American Academy of Sleep Medicine's Board of Directors. Mr. Heald is employed by the American Academy of Sleep Medicine. The other authors have indicated no financial conflicts of interest.

## Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

## Guideline Availability

2012 Guideline

Available from the American Academy of Sleep Medicine (AASM) Web site .

2016 Focused Update

Available from the AASM Web site .

## Availability of Companion Documents

The following is available:

- 2016 sleep medicine trends: central sleep apnea - when is this important? Continuing medical education activity. Available from the American Academy of Sleep Medicine (AASM) Web site .

## Patient Resources

None available

## NGC Status

This NGC summary was completed by ECRI Institute on April 20, 2012. The information was verified by the guideline developer on May 17, 2012. This summary was updated by ECRI Institute on January 23, 2013 following the U.S. Food and Drug Administration advisory on Zolpidem containing products. This summary was updated by ECRI Institute on September 23, 2016. The information was verified by the guideline developer on October 6, 2016.

## Copyright Statement



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